WHY DO BABIES DIE?
AN OVERVIEW OF RESEARCH INTO STILLBIRTHS AND NEONATAL DEATH

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Disclaimer

- I currently have grant funding from Tommy’s – The Baby Charity, Holly Martin Stillbirth Research Fund and Action Medical Research for investigations into the placenta and stillbirth, management of reduced fetal movements and improving care in subsequent pregnancies after stillbirth.

- I am on the board of the International Stillbirth Alliance
Important Definitions

- **Stillbirth**
  - UK - birth of an infant with no signs of life after 24 weeks gestation
  - WHO - birth of an infant with no signs of life after 22 weeks gestation or 500g
  - WHO - late stillbirth 28 weeks or 1000g

- **Neonatal Death**
  - UK – death of a live born infant in 1st 28 days of life
  - Early – < 7 days
  - Later – 7-27 days of age

- **Perinatal Death**
  - Stillbirths + Early Neonatal Deaths
Stillbirth in the UK

- In 2008, 4,043 stillbirths (5.2/1,000 live births)
- In 2011, 4,400 stillbirths

- 33 / 35 high-income countries
Neonatal Death in the UK

- Reduction in neonatal death over 8 year period.
  - Early NND have seen greatest improvement
Perinatal Mortality

- Reduced from 2000 to 2008
Are we making progress?

- Stillbirth rate shows much slower decrease than neonatal death
  - 1.1% per year vs. 2.1%

- The ratio of stillbirth : neonatal death used to be 50%:50%, now approximately 60%:40%

- Yes and No
Stillbirth rates

- Little overall change in stillbirth rates
- May be alterations in underlying causes
- To effectively reduce stillbirths, essential to understand the cause
- Cause vs. association
Has stillbirth changed?

Primary ReCoDe

N=281

N=81
Has stillbirth changed?

Secondary ReCoDe

MEDICAL DISORDERS
PLACENTAL INSUFFICIENCY

1986-1996 N=281
2009-2011 N=81
Which factors are related to perinatal mortality?

- Drug Use
- Low Socioeconomic Group
- Ethnic Minorities
- Reduced fetal movements
- Increased Maternal Age
- High AFP Low PAPP-A
- Teenagers
- Excessive Alcohol
- Smokers
- English not first language
- Diabetes
- IUGR
- Poor educational attainment
- Hypertension
- Congenital Anomaly
- Thrombophilia
- Previous Stillbirth / NND
- Renal disease
Can we do anything? – Learning Lessons

- In 1993 there were 190 road traffic deaths in Wales, there are now 89.
- In 1993 there were 215 stillbirths in Wales, there are now 180.
Why no improvement in stillbirths (and only a modest improvement in NND)?

- **Hidden problem**
  - Social taboo
  - Costs

- **Multifactorial**
  - Where to start?
  - Insufficient research to guide practice
  - Decrease in investigations to understand stillbirth/NND

- **Delivery**
  - Difficult to administer UK-wide Guidelines / Protocols
  - Cost
How could we reduce perinatal deaths?

- Do what we know works
- Stop cigarette smoking (PAR 4-7%)
- Robust perinatal audit
  - Demonstrated to reduce perinatal and maternal mortality
    - Alderleisten, et al. EuJOGRB, 2008; Netherlands
    - Dahl et al. Acta Obstetricia, 2000; Norway
    - Pattinson et al. IJGO, 2009; LMICs
    - Belizan et al. BMC Health Serv Res, 2011; South Africa
- Risk stratify women appropriately
  - Continuously reassess risk
## Confidential Enquiries

<table>
<thead>
<tr>
<th>Type of Avoidable Factor</th>
<th>Number (%)</th>
<th>NCUH (%)</th>
<th>UHMB (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Related to healthcare professionals</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-pregnancy or preconception care</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Assessment or point of entry to care</td>
<td>12 (31.6)</td>
<td>8 (40)</td>
<td>4 (22.2)</td>
</tr>
<tr>
<td>Diagnosis or in the recognition of high-risk status</td>
<td>21 (55.3)</td>
<td>10 (50)</td>
<td>11 (61.1)</td>
</tr>
<tr>
<td>Referral to a specialist</td>
<td>15 (39.5)</td>
<td>8 (40)</td>
<td>7 (38.9)</td>
</tr>
<tr>
<td>Treatment</td>
<td>25 (65.8)</td>
<td>13 (65)</td>
<td>12 (66.7)</td>
</tr>
<tr>
<td>Clinical leadership</td>
<td>13 (34.2)</td>
<td>7 (35)</td>
<td>6 (33.3)</td>
</tr>
<tr>
<td>Education, knowledge and training</td>
<td>29 (76.3)</td>
<td>15 (75)</td>
<td>14 (77.8)</td>
</tr>
<tr>
<td>Documentation</td>
<td>23 (60.5)</td>
<td>11 (55)</td>
<td>12 (66.7)</td>
</tr>
<tr>
<td>Discharge or transfer from care</td>
<td>17 (44.7)</td>
<td>9 (45)</td>
<td>8 (44.4)</td>
</tr>
<tr>
<td><strong>Related to services</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Communication</td>
<td>14 (36.8)</td>
<td>6 (30)</td>
<td>8 (44.4)</td>
</tr>
<tr>
<td>Policies and procedures</td>
<td>5 (13.2)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Related to the woman or her family</td>
<td>4 (10.5)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>
Insufficient Research

Year

2008
2007
2006
2005
2004
2003
2002
2001
2000
1999
1998
1997
1996
1995
1994
1993
1992
1991
1990

Number of Citations

Stillbirth
Ovarian Cancer
Total Publications x1000

Insufficient Research
Insufficient understanding of perinatal deaths?

• Why investigate perinatal deaths?
• Medical
  – Increased probability of problems in future pregnancies (2-10 fold)
  – Ensure that care optimal
  – Quality of information for patients
• Psychological

Table 2. Parents’ reasons for having a postmortem examination

<table>
<thead>
<tr>
<th>Reasons</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professional advice</td>
<td>102 (22.2%; 18.4–26.0)</td>
</tr>
<tr>
<td>Cause for child’s death</td>
<td>336 (73.0%; 68.9–77.1)</td>
</tr>
<tr>
<td>Reduce other babies dying in future</td>
<td>228 (49.6%; 45.0–54.2)</td>
</tr>
<tr>
<td>Research</td>
<td>197 (42.8%; 38.3–47.3)</td>
</tr>
</tbody>
</table>
National Perinatal Audit

- CMACE (closed 2010)
  - Funded by National Patient Safety Agency
  - 4 roles (The CEMACH Programme):
    - Maternal death enquiry
    - National perinatal and maternal mortality surveillance
    - Maternal and perinatal enquiry projects
    - Child health enquiry projects
- To be replaced by MMBRACE (2013)
  - NPEU-led collaboration
Confidential Enquiry Into Stillbirth and Deaths in Infancy (CESDI)

- Set up in 1992 in response to high perinatal mortality rates
- Notification system of all deaths after 20 weeks gestation until 1 year of life
- Produced various specialist reports e.g. Project 27/28, Shoulder dystocia, Intrapartum Deaths
- From 2003 part of the Confidential Enquiry into Maternal and Child Health
- Collects details of all deaths from 22 weeks gestation until 28 days of life
Understanding Perinatal Death

- Difficulty in determining “cause” of death (particularly true of stillbirths)

- Limited by the data available
  - Low rate of PM (especially after NND)

- Classification systems varied
  - At least 35 classification systems in use
# The Value of Investigations after Perinatal Death

<table>
<thead>
<tr>
<th>Test</th>
<th>Information</th>
<th>Unique Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-mortem</td>
<td>57-74%</td>
<td>9-34%</td>
</tr>
<tr>
<td>MRI</td>
<td>17%</td>
<td>-</td>
</tr>
<tr>
<td>Placental histology</td>
<td>58-84%</td>
<td>16-19%</td>
</tr>
<tr>
<td>Chromosomal analysis</td>
<td>5-10%</td>
<td>-</td>
</tr>
<tr>
<td>Blood tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycosylated Hb</td>
<td>&lt;5%</td>
<td>*</td>
</tr>
<tr>
<td>Thrombophilia screen</td>
<td>10-15%</td>
<td>*</td>
</tr>
<tr>
<td>Cholestasis</td>
<td>&lt;1%</td>
<td>*</td>
</tr>
</tbody>
</table>

* No robust studies
**Conceptual model**

**Fetal**
- Congenital Anomaly
- Small for gestational age
- Fetal growth restriction
- Large for gestational age
- Reduced placental blood flow

**Maternal**
- High BMI
- Maternal age
- Hypertension
- Diabetes
- Ethnicity

**Environment/stressor**
- Late gestation
- Smoke exposure
- Infection
- Poverty
- Diet

**Perinatal Death**
Causes of Stillbirth
Causes of NND

Figure 6.2
Primary cause/associated factor of neonatal deaths using the CMACE maternal and fetal classification; England, Wales, Northern Ireland and the Crown Dependencies: 2008 (excluding terminations of pregnancy)

Associated obstetric factors

- Premature rupture of membranes: 9.2%
- Intrapartum asphyxia: 3.9%
- Polyhydramnios: 0.5%
- Oligohydramnios: 1.2%
- Other associated obstetric factor: 3.9%
- Birth injury to scalp: 0.1%
- Other birth trauma: 0.3%
- Intracranial haemorrhage: 0.5%

Total associated obstetric factors: 17.3%
Searching for a cause (or not) of Perinatal Death

- Post-mortem remains the gold standard investigation
  - 42.4% of stillbirths
  - 22.9% of NND

Table 6.9
Proportions of placental histology among stillbirths, perinatal and neonatal deaths; England, Wales, Northern Ireland and the Crown Dependencies: 2008

<table>
<thead>
<tr>
<th></th>
<th>Stillbirths N=3,730</th>
<th>Perinatal deaths N=5,597</th>
<th>Neonatal deaths N=2,396</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placenta sent for histology</td>
<td>2,998 (80.4)</td>
<td>3,962 (70.8)</td>
<td>1,110 (46.3)</td>
</tr>
<tr>
<td>Placenta sent for histology and details received at CMACE</td>
<td>1,432 (38.4)</td>
<td>1,785 (31.9)</td>
<td>408 (17)</td>
</tr>
<tr>
<td>Placenta not sent for histology</td>
<td>471 (12.6)</td>
<td>1135 (20.3)</td>
<td>936 (39.1)</td>
</tr>
<tr>
<td>Not known if placenta was sent for histology</td>
<td>261 (7.0)</td>
<td>500 (8.9)</td>
<td>350 (14.6)</td>
</tr>
</tbody>
</table>

Source: CMACE
Insufficient investigation

- Consent given for PM decreasing
- Increased proportion of “unexplained” stillbirths
Investigation after Neonatal Death

- Larger proportion of coroner PMs
- Greater proportion of PMs declined and not offered compared to stillbirth
Addressing Investigation of Perinatal Deaths

- Introduction of guidelines
- Counselling by senior obstetrician / midwife

Stock et al. 2010
EuJOGRB
Impact of Carers on Consent Process for Investigations

- Neonatal Death

C Rose, M Evans, J Tooley
Falling rates of perinatal postmortem examination: are we to blame?
Arch Dis Child Fetal Neonatal Ed 2006 91: F465
A difficult conversation? The views and


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Post-mortem examination after stillbirth: views of UK-based practitioners

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ABSTRACT

Objectives: Worldwide, around four million stillbirths occur annually. The UK was recently ranked as 33rd out of 35 developed nations for stillbirth rates. The reasons for many stillbirths remain unexplained. Post-mortem examination (PME) can provide information for grieving families, and for future pregnancies. Rates of consent for PME are decreasing in the UK. The views of professionals may influence their approach to bereaved families, and, therefore, rates of consent. Arguably, obtaining qualitative insights
Barriers to Consent for PM

- Some important differences in the perception of barriers to PM consent
- Majority agree:
  - Emotional distress
  - Child being moved to another unit
- Majority disagree:
  - Lack of rapport with staff
  - Staff workload
  - Religion / Culture
  - Negative press publicity
- Studies being repeated in NND
- [http://www.surveymonkey.com/s/neonatalprofessionals](http://www.surveymonkey.com/s/neonatalprofessionals)
Importance of Placental Evaluation

- Recommended for all stillbirths by RCOG, ACOG & PSANZ
- International recognition that histological examination of the placenta needs to be developed
Basic Information from Placentas

- Placental size is reduced in placentas from stillbirths
- There is an increase in fetal:placental weight ratio in placental stillbirths and “unknown” stillbirths

Heazell and Martindale, JOG, 2009
Is Placental Histology Useful?

- Histological assessment of the placenta is one of the most common (80%) and cost-effective investigations to determine the cause of stillbirth (£102 per “positive” test)
- Histological examination of the placenta reduces the chance of having an “unexplained stillbirth” (OR 0.17, 95% CI 0.04-0.7)
- Some placental features are related to specific causes of stillbirth

Heazell et al. Arch Dis Child 2011;96(Suppl I): Fa135
Heazell & Martindale, JOG, 2009;29(3):225—228
Placental changes in stillbirth

- Tissue bank in CMFT Dept Histopathology
- Found cases of stillbirths with an established cause after post-mortem examination – IUGR, infection, hypertension, diabetes and cord pathology
- Compared to stillbirths of “unknown” cause
- Stained for CD45 (inflammation), CD31 (vascularity), Ki67 (proliferation) and CK7 (trophoblast).
Syncytial Nuclear Aggregates

Heazell, Unpublished data, 2012
Proliferation

![Graph showing proliferative index](image)

Normalized Live Birth

- Normal
- Cord accident
- Hypertension
- IUGR

Heazell, Unpublished data, 2012
Vascularity

Villous Vascularity

Avascular Villi

Normal Live Birth  Cord  Hypertension  IUGR

Heazell, Unpublished data, 2012
### Placental Phenotype in Stillbirth

In stillbirths IUGR has a **distinct** phenotype:
- **Reduced** proliferation, **Reduced** vascularity, **Thickened** trophoblast
- If applied to placentas from stillbirths of unknown cause 2 had the same placental phenotype

<table>
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<th>SNA</th>
<th>Proliferation</th>
<th>Vascularity</th>
<th>Avascular Villi</th>
<th>Trophoblast</th>
<th>Leukocytes</th>
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<td>High</td>
<td>High</td>
<td>Unchanged</td>
<td>IUGR</td>
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<tr>
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<td>High</td>
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<td>Low</td>
<td>High</td>
<td>High</td>
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<td>IUGR</td>
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<td>Low</td>
<td>High</td>
<td>Increased</td>
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<td>Increased</td>
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</table>

Heazell, Unpublished data, 2012
### Importance of Placental Research

<table>
<thead>
<tr>
<th>Research Priority</th>
<th>Rank (weighted/unweighted)</th>
<th>RPS (weighted)</th>
<th>RPS (unweighted)</th>
<th>AEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>The effects of periconceptual environment, including nutrition and micronutrient status, on embryonic development</td>
<td>1 (1)</td>
<td>82.2</td>
<td>80.9</td>
<td>0.79</td>
</tr>
<tr>
<td>Development of repositories of well phenotyped human samples from stillbirths or other related conditions and matched controls, with clear arrangements for access, and appropriate ethical and other legal permissions in place</td>
<td>2 (2)</td>
<td>82.1</td>
<td>78.0</td>
<td>0.70</td>
</tr>
<tr>
<td>Characterising the fetal response to an adverse intrauterine environment to develop improved means of clinical assessment of fetal wellbeing</td>
<td>3 (5)</td>
<td>80.3</td>
<td>74.9</td>
<td>0.68</td>
</tr>
<tr>
<td>Defining pathophysiological pathways leading to stillbirth associated with maternal disease, in particular type 1 and type 2 diabetes mellitus</td>
<td>4 (3)</td>
<td>79.3</td>
<td>76.5</td>
<td>0.70</td>
</tr>
<tr>
<td>Defining pathophysiological pathways leading to increased rates of growth restriction and decreased rates of pre-eclampsia among smokers</td>
<td>5 (6)</td>
<td>79.0</td>
<td>74.8</td>
<td>0.70</td>
</tr>
<tr>
<td>Development of improved statistical, biometric, and bioinformatic technologies for data interpretation and clinical prediction of outcome</td>
<td>6 (4)</td>
<td>76.6</td>
<td>76.3</td>
<td>0.67</td>
</tr>
<tr>
<td>The effect of maternal obesity, with or without insulin resistance, on fetal and placental development</td>
<td>7 (7)</td>
<td>74.8</td>
<td>72.5</td>
<td>0.71</td>
</tr>
<tr>
<td>The role of normal and abnormal coagulation in normal and abnormal pregnancy</td>
<td>8 (8)</td>
<td>73.7</td>
<td>71.9</td>
<td>0.78</td>
</tr>
<tr>
<td>Understanding the fetal or placental function and control of the timing of parturition in post-dates pregnancy</td>
<td>9 (9)</td>
<td>72.7</td>
<td>70.8</td>
<td>0.67</td>
</tr>
<tr>
<td>Discovery-based analysis (expression array or high throughput sequencing, proteomics, and metabolomics) of samples from well characterised complicated pregnancies and matched controls</td>
<td>10 (12)</td>
<td>70.9</td>
<td>64.5</td>
<td>0.63</td>
</tr>
</tbody>
</table>

RPS = research priority score. AEA = average expert agreement. All scores are out of 100, apart from AEA which ranged from 0.50 to 0.79.

*Table 2: Top ten research priorities in discovery science*
Local Perinatal Audit and Investigations

- Declining stillbirth and neonatal death rates
- Above national average, if tertiary referrals removed
  - NND 1.7 per 1,000 live births
  - SB 4.5 per 1,000 live births
Investigations after Perinatal Death

- Post-mortem
  - 19% after NND
  - 39% after Stillbirth
  - Contributed useful information to the case of death in 83% of SBs and all NNDs

- Placental histology
  - 41% after NND
  - 74% after SB
  - Contributed useful information in 90% of SBs and 91% of NNDs
Birthweight Centile – SB and NND

Stillbirths

Neonatal Deaths
Factors Associated with Stillbirths
Factors Associated with NND

- No “unexplained” NNDs
Lessons learnt from Perinatal Review

- Understand why babies die – local, regional and national
- Adapt and develop relevant models of care
- Attempt to gain as much information as possible (history, examination, investigation)
- Apply modern classification system
  - CODAC, ReCoDe, TULIP
- Benchmarking
Summary

- Perinatal death is a significant challenge in maternity care
- There are significant overlaps in causes of stillbirth and neonatal death
- Information is important – Why do babies die?
- Ensure that care is the best standard to prevent perinatal death
- Develop new pathways/tests / strategies to reduce perinatal mortality (while not significantly increasing morbidity)
Acknowledgements

- Professor Colin Sibley
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EVERYONE IN THE MATERNAL AND FETAL HEALTH RESEARCH CENTRE